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A review of cytokine structures

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Abstract. The expanding family of cytokines, interleukins and colony-stimulatory factors has made it difficult to readily access their structural and biological properties for comparative purposes. Here their aligned amino acid sequences, biological actions and some structural predictions are presented together for ready comparisons

Introduction

Cytokines, interleukins and colony-stimulating factors are a family of regulatory polypeptides involved in host defence and share a number of features in common.

1. Unlike most of the classical endocrine hormones, cytokines rarely circulate in the blood at biologically significant levels in normal animals but are induced acutely in response to infection, antigenic stimulation or tissue injury and are rapidly cleared from their site of action. They are rarely produced by single organs in response to a single type of stimulus but rather are produced by multiple types of cells scattered throughout the body in response to a variety of different inflammatory signals. The production and action of cytokines is often highly localized to inflammatory sites, being paracrine (cells adjacent to the effector cell produce the cytokine) or autocrine (effector cells produce the cytokine themselves) rather than endocrine.

2. The production and action of the cytokines is intricately organized with what appears to be a great deal of redundancy and amplification. Many cell types (in particular T-lymphocytes, macrophages, endothelial and fibroblastic cells) produce and secrete a large variety of different cytokines in response to bacterial products or antigenic stimulation. The cytokines themselves have overlapping actions (redundancy) on a variety of effector cells (pleiotropy) and, moreover, form a cascade system where one cytokine can induce the production of several others (amplification) or increase the response to others (synergy).

3. Because they function extracellularly as communicators between cells often in hostile environments, the cytokines generally have the following characteristics. They are small proteins, usually glycosylated and their conformation is maintained by intra-molecular and sometimes inter-molecular disulfide bonds. This endows the cytokines with an often remarkable stability to changes in pH, ionic strength, denaturants and proteases. The cytokines are uniformly active at very low concentrations (generally a few picomolar to a few hundred picomolar) and bind to cell surface receptors with a very high affinity.

4. In addition to stimulating a variety of different cell types, the cytokines often exert multiple levels of regulation on cells of the same cell lineage. For example the colony-stimulating factors are required for the survival, proliferation and differentiation of blood cell precursors but also stimulate various functional activities of the mature white blood cells in the blood and tissues that are involved with host defence.

5. Nineteen amino acid sequences of human and murine hemopoietins have been analyzed using algorithms predictive for secondary structure [1, 2]. The results suggest that they each contain a 4-α-helical bundle, about 2–5 nm long, as a common conformational feature.

Abbreviations: BCGF, B-cell growth factor; BSF – 1, B-cell stimulating factor; CNDF, cholinergic neuronal differentiation factor; CSF, colony-stimulating factor; CSIF, cytokine synthesis inhibitory factor; DIA, differentiation inhibitory activity; DRF, differentiation retarding factor; EDF, eosinophil differentiation factor; EPO, erythropoietin; G, granulocyte; HILDA, human interleukin for DA-1 cells; HP.1, hybridoma/plasmacytoma growth factor; HSF, hepatocyte stimulating factor; IFN, interferon; IL, interleukin; LIF, leukemia inhibitory factor; M, macrophage; MCGF, mast cell growth factor; MGI, macrophage-granulocyte inducer; MLPLI, melanoma-derived lipoprotein lipase inhibitor; TCGF, T-cell growth factor; TNF, tumor necrosis factor; TRF, T-cell replacing factor

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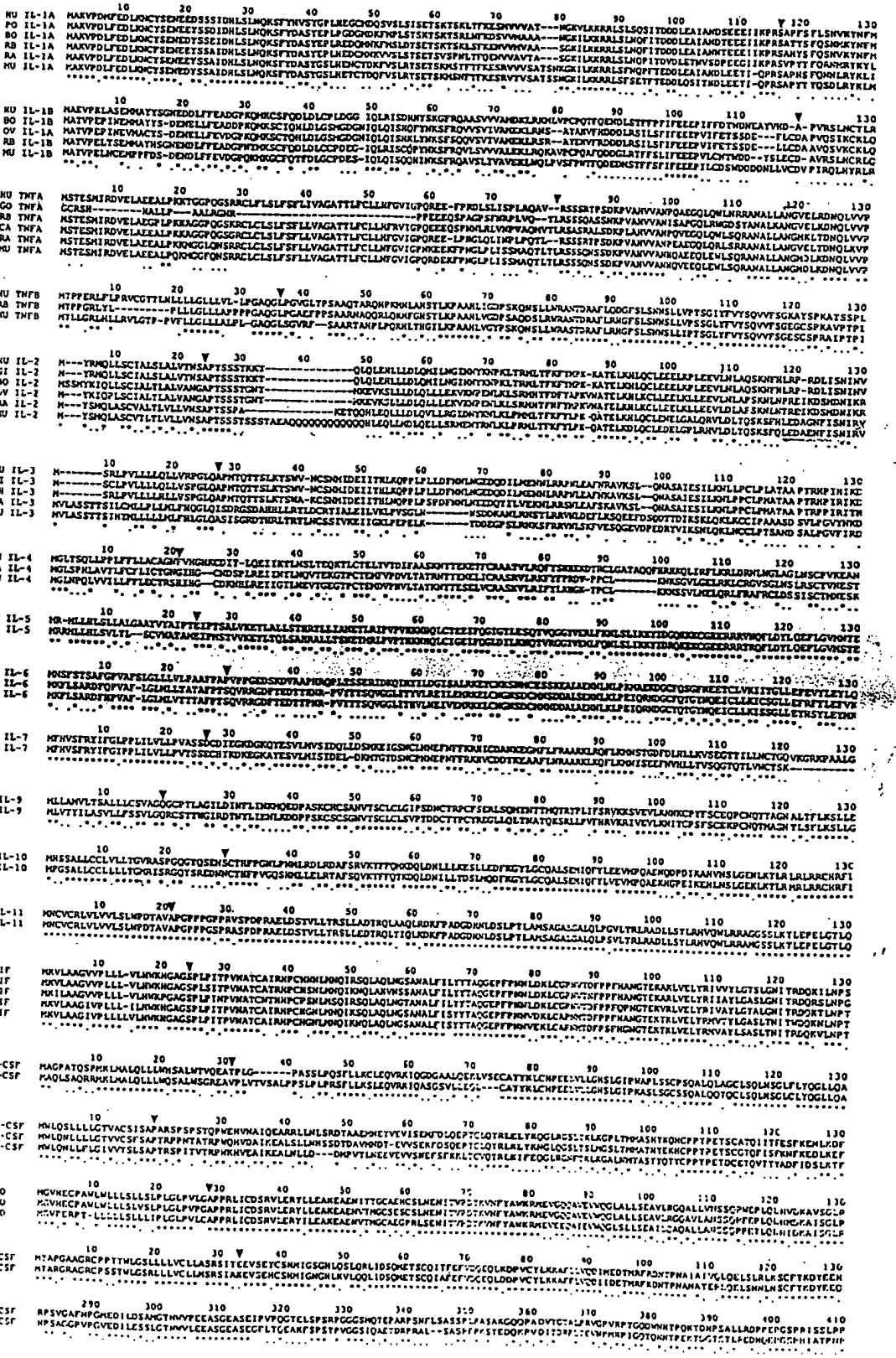
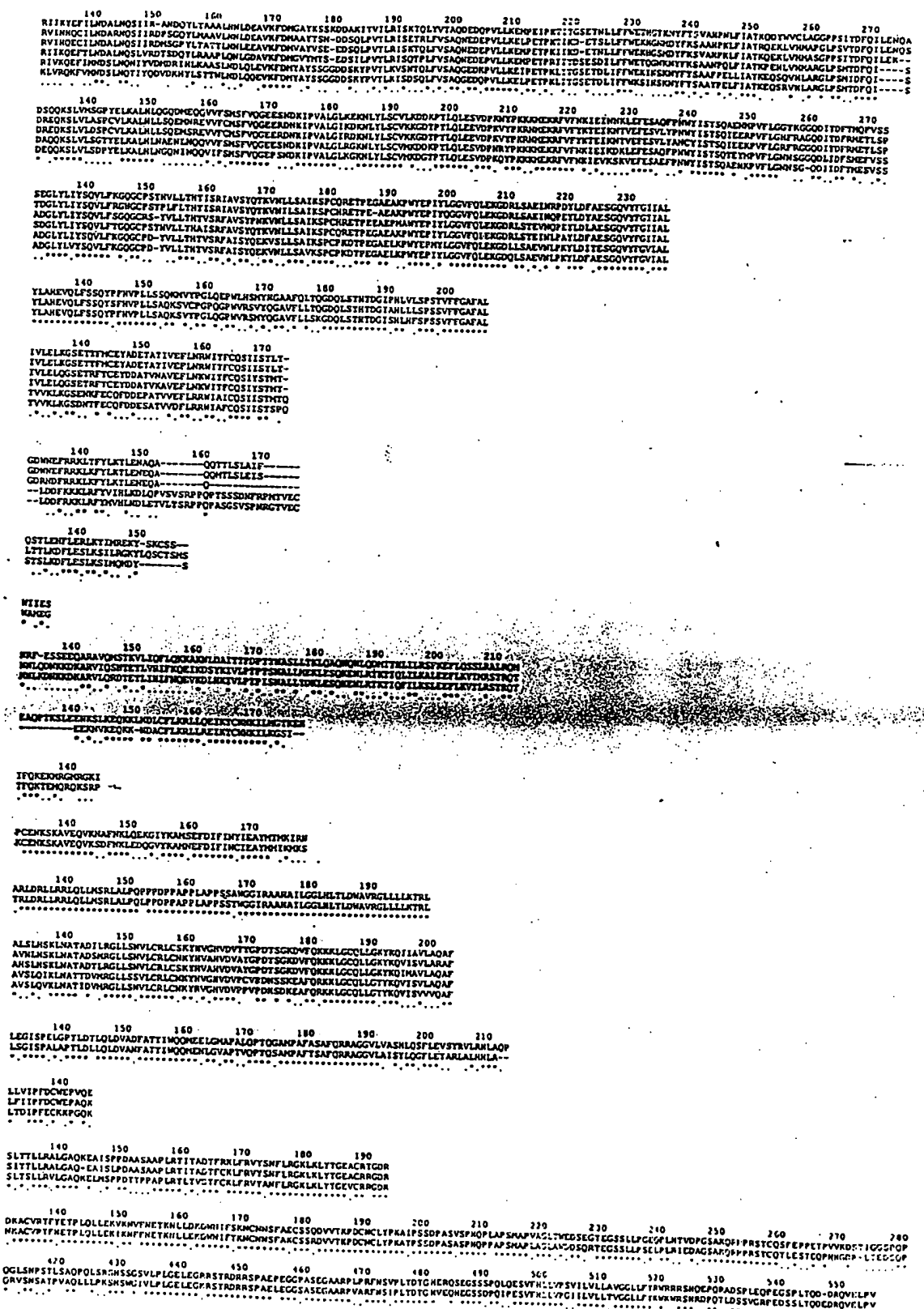


Fig. 1. Aligned amino acid sequences for 18 different hemopoietins of the 12 species for which data are available. * Identity between all sequences



of the mature human sequence. *Hu* Human; *Rh* Rhesus monkey; *Gi* Gibbon, *Mu* cynomologous monkey; *Po.* porcine (pig); *Bo* bovine (cow); *Ov* ovine (sheep); *Go* goat; *Rb* rabbit; *Ca* cat; *Ra* rat; *Mu* murine (mouse)

Table 1. Molecular properties of cytokines

Interleukins and cytokines	Other names	Species	Subunits	Leader[a]	Mature protein[b] M_r ($\times 10^{-3}$) (N)	Cysteines[c]	*N*-Glycosylation[d] sites	Glycosylated M_r ($\times 10^{-3}$)	References
IL-1α		Murine	1	114	17.9–19.0 (156)	–	–	–	[17]
IL-1α		Human	1	112	17.5 (159)	141	–	–	[18–20]
IL-1β		Murine	1	117	17.5 (152)	71	–	–	[21]
IL-1β		Human	1	116	17.5 (153)	8, 71	–	–	[22–25]
TNFα		Murine	1	79	17.0 (156)	69–100	–	–	[26, 27]
TNFα		Human	1	76	17.0 (157)	69–101	–	–	[28, 29]
TNFβ	Lymphotoxin	Murine	1	34	18.5 (169)	83	60	20–25	[30–32]
TNFβ	Lymphotoxin	Human	1	34	18.5 (171)	–	62	20–25	[33]
IL-2		Murine	1	20	19.4 (149)	72–120	–	–	[34–36]
IL-2		Human	1	20	17.6 (133)	58–105	–	–	[37–41]
IL-3	Multi CSF	Murine	1	26	16.2 (140)	17–79, 80–140 i	N16, 51, 86+O	18–30	[42–44]
IL-3	Multi CSF	Human	1	19	15.4 (133)	16–84i	N 15, 70+0	15–30	[45, 46]
IL-4	BSF-1, MCGF, TCGF	Murine	1	20	14.0 (120)	5–87, 27–67, 49–94	N 41, 71, 97	15–19	[47, 48]
IL-4	BSF-1, MCGF, TCGF	Human	1	24	15.0 (129)	3–127, 24–65, 46–99	N 35, 105	15–19	[49]
IL-5	EDF, BCGF II, TRF	Murine	2	21	13.3 (112)	41–83	N 25, 54, 68	32–62	[50]
IL-5	EDF, BCGF II, TRF	Human	2	22	13.2 (112)	41–83	N 25, 68	46	[51–53]
IL-6	BSF-2, IFN-β_2, HP1	Murine	1	24	21.7 (187)	46–52, 75–85	O 143	22–29	[54–58]
IL-6	HSF, 26 KD	Human	1	28	20.8 (184)	44–50, 73–83i	N 45, 0143	19–21	[59, 60]
IL-7		Murine	1	25	14.9 (131)	2, 33, 46, 91, 108, 120	N 69, 90	25	[61]
IL-7		Human	1	25	17.4 (153)	2, 34, 47, 92, 129, 141	N 70, 91, 116		[62, 63]
IL-9, P40	Mast cell-enhancing factor	Murine	1	18	14.15 (126)	3, 27, 29, 36, 38, 46, 50, 86, 91, 95	N 32, 60, 83, 96	38–40	[64]
IL-9/P40		Human	1	18	14.11 (126)	3, 27, 29, 36, 38, 46, 50, 86, 91, 95	N 32, 45, 60, 96		[65]
IL-10	CSIF	Murine	1	18	18.7 (160)	2, 52, 98, 104, 149	N16, 116	17–21	[66]
IL-11		Human	1	17–20	20.0–23.0 (182–179)		–	–	[67]
LIF	CNDF, D-factor DRF, DIA	Murine	1	24	20.0 (179)	11–133, 17–130, 59–162	N 9, 34, 63, 73	45–62	[68, 69]
LIF	DIF, HILDA, HSF III, MLPLI	Human	1	22	20.0 (181)	11–133, 17–130, 59–162	N 9, 34, 63, 73	32–45	[70]
G-CSF	MGI-1G	Murine	1	30	19.1 (178)	42–48, 70–80i	O 139	25	[71]
G-CSF	CSF-β, Pluripoietin	Human	1	30	18.6 (177)	39–45, 67–77	O 133	20	[72–74]
GM-CSF	MGI-1GM Pluripoietin-α	Murine	1	17	14.4 (124)	51–93, 85–118i	N 58, 67+0	18–25	[75]

Table 1 (continued)

Interleukins and cytokines	Other names	Species	Subunits	Leader[a]	Mature protein[b] M_r ($\times 10^{-3}$) (N)	Cysteines[c]	*N*-Glycosylation[d] sites	Glycosylated M_r ($\times 10^{-3}$)	References
GM-CSF	CSF-α	Human	1	17	14.7 (127)	54–96, 88–121i	N 19, 29+0	18–30	[76, 77]
EPO	–	Murine	1	26	18.4 (167)	7, 139, 162	N 24, 38, 83	29.9	[78]
EPO		Human	1	27	18.4 (166)	7–161, 29–33	N 24, 38, 83	29.9	[79, 80]
M-CSF	MGI-1M, CSF-1	Murine	2	31	21 (189), 18 (158)	7, 31, 48, 90, 102, 139, 146o	N 122, 140+0	70–90, 45–50	[81]
M-CSF	CSF-1	Human	2	32	21 (189), 18 (158)	7, 31, 48, 90, 102, 139, 146o	N 122, 140+0	70–90, 45–90	[82–84]

[a] Number of amino acids in putative leader sequence
[b] Molecular weight and number of amino acids (*N*) in the protein core of the mature protein
[c] 1-2 cystine amino acid positions are linked with a dash where known; i, intramolecular; o, intermolecular
[d] Positions of potential *N*-linked glycosylation sites (N) or known *O*-glycosylation sites (O)
[e] Three alternate transcripts, each a disulfide-bonded dimer, exist both as transmembrane and proteolytically released forms
[f] References for cytokines of other species can be found in ([85–112], and G. Willson and N.M. Gough, personal communication)

Results

Here we present the aligned amino acid sequences (Fig. 1) and some structural determinants of cytokines of different species (Table 1) to provide ready access for structural and mutagenesis studies. The detailed biology, biochemistry and molecular biology of these cytokines can be addressed through several recent reviews [3–12, 13] and through Table 2. The predicted structures of several cytokines as 4-α-helical bundles are summarized in Table 3. The cytokine family is expanding rapidly and already producing subfamilies – some of these, including the interferons, transforming growth factors β and the interleukin-8 family, are excluded from the present listing but can be found in the following references [14–16].

Table 2. Biological functions of the cytokines

IL-1α and β	Activates T-cells by inducing IL-2 release
	Co-factor for B-cell proliferation and differentiation
	Induces GM-CSF, G-CSF and IL-6 production by bone marrow stroma
	Stimulates fibroblast proliferation and prostaglandin and collagen synthesis by stroma
	Induces acute-phase protein release by liver hepatocytes
	Stimulates bone resorption and cartilage breakdown
	Induces fever
	Produced by macrophages, endothelial cells, fibroblasts
TNFα and β	Stimulates T- and B-cell proliferation
	Induces IL-1α, IL-1β, IL-6, GM-CSF and G-CSF production by stroma
	Mediator of cachexia (weight loss) and fever
	Other actions similar to IL-1
	Produced by macrophages, endothelial cells and fibroblasts
IL-2	Stimulates T-cell proliferation
	Stimulates B-cell proliferation and differentiation
	Stimulates natural killer cell proliferation and killing capacity
	Increases cytotoxic capacity of macrophages
	Produced by activated T-cells
IL-3	Stimulates proliferation and differentiation of precursors for granulocytes, macrophages, eosinophils, megakaryocytes, erythroid cells and mast cells
	Enhances cytotoxic capacity of macrophages and eosinophils
	Produced by activated T-cells
IL-4	Stimulates T-cell proliferation
	Enhances differentiation of B-cells (immunoglobin switching, Ia antigen and Fc receptor expression)
	Stimulates mast cell growth
	Modulates state of activity of macrophages
	Produced by activated T-cells
IL-5	Stimulates proliferation and differentiation of eosinophil precursors
	Stimulates B-cell growth and enhances immunoglobulin production
	Produced by activated T-cells

Table 2 (continued)

IL-6	Stimulates plasmacytoma cell growth Stimulates immunoglobulin synthesis by B-cells Induces IL-2 production by T-cells Acts as a growth factor for neutrophilic, megakaryocytic and early precursor cells Induces acute phase response from liver hepatocytes Nerve cell differentiation factor Produced by endothelial cells, fibroblasts, macrophages		Stimulation of hepatic release of acute phase proteins Inhibition of differentiation in embryonic stem cell lines Stimulation of osteoblast function Adrenergic to cholinergic transmitter switching in some neurons Inhibition of lipoprotein lipase activity in adipocyte lines
IL-7	Induces proliferation of precursor B-cells and T-cells Produced by hemopoietic stroma	Epo	Produced by fibroblasts, macrophages and glial cells Production of erythrocytes and megakaryocytes
IL-9	Induces proliferation of helper T-cells Stimulates mast cell and megakaryocyte progenitor cell growth Produced by activated T-cells	G-CSF	Produced by kidney epithelium and macrophages Stimulates proliferation and differentiation of neutrophilic granulocyte precursors Activates granulocyte cytotoxic function Chemotactic for endothelial cells
IL-10	Inhibits the synthesis of cytokines by activated T-cells Inhibits some immune reactions Stimulates mast cell growth Produced by activated T-cells	GM-CSF	Produced by macrophages, endothelial and fibroblasts Stimulates proliferation and differentiation of neutrophil, eosinophil, macrophage, megakaryocyte and erythroid precursor cells Mitogenic for endothelial, fibroblast, osteoblast and trophoblastic cells Activates cytotoxic function of neutrophils, eosinophils and macrophages
IL-11	Stimulates the proliferation of an IL-6-dependent plasmacytoma cell line Stimulates the T-cell-dependent development of immunoglobulin producing B-cells and synergizes with IL-3 in supporting murine megakaryocyte colony formation Regulator in the hematopoietic microenvironment Produced by hemopoietic stroma	M-CSF	Produced by activated T-cells, macrophages, endothelial cells and fibroblasts Stimulates proliferation and differentiation of macrophage precursor cells Activates cytotoxic function of macrophages Required for production of osteoclasts May have activity on trophoblasts
LIF	Differentiation induction and suppression of the proliferation of some leukemic cell lines Synergistic stimulation of megakaryocyte and platelet production		Produced by fibroblasts and macrophages

Table 3. Predicted 4α-helical bundle structures for 19 cytokine sequences. Using the helical predictions of Chou and Fasman [113] and Garnier et al. [114] and the heptad algorithm [1, 2, 115, 116] for the 19 Hu and Mu hemopoietins, we summarize the locations of amino acid sequences of the various putative secondary structures of the four helical elements of the bundles. The locations and nomenclatures of the helices, N and C termini as well as the loops between the four helical elements of the bundles are shown in this table [1, 2]. The amino acid numberings are for the mature cytokine sequences (that is starting after the cleavage sites in Fig. 1)

Cytokines	N termini	A helix	Loop 1	B helix	Loop 2	C helix	Loop 3	D helix	C terminus
Hu IL-2	1–32	33–56	57–65	66–78	79–82	83–101	102–116	117–133	–
Mu IL-2	1–46	47–70	71–79	80–92	93–97	98–116	117–131	132–148	149
Hu IL3	1–18	19–27	28–55	56–68	69–70	71–85	86–102	103–121	122–133
Mu IL-3	1–19	20–28	29–49	50–62	63–66	67–81	82–96	97–115	116–140
Hu IL-4	1–6	7–22	23–43	44–59	60–79	80–95	96–109	110–123	124–130
Mu IL-4	1–5	6–21	22–42	43–58	59–70	71–86	87–100	101–114	115–117
Hu IL-5	1–6	7–22	23–42	43–58	59–61	62–78	79–92	93–110	111–112
Mu IL-5	1–6	7–22	23–42	43–58	59–61	62–78	79–92	93–110	111–112
Hu IL-6	1–24	25–41	42–83	84–105	106–144	145–165	–	166–184	–
Mu IL-6	1–26	27–43	44–85	86–107	108–147	148–168	–	169–187	–
Hu IL-7	1–10	11–28	29–51	52–59	70–73	74–90	91–126	127–148	149–152
Mu IL-7	1–10	11–28	29–50	51–68	69–72	73–89	90–105	106–127	128–129
Hu G-CSF	1–12	13–26,	27–48,	70–97	98–105	106–130	131–154	155–175	176–177
Mu G-CSF	1–18	49–57 19–32, 52–60	58–69 33–51 61–72	73–100	101–108	109–133	134–157	158–178	
Hu GM-CSF	1–14	15–28	29–33	34–49	50–54	55–75	76–96	97–117	118–127
Mu GM-CSF	1–14	15–28	29–30	31–46	47–51	52–72	73–93	94–114	115–124
Hu EPO	1–2	3–20	21–54	55–77	78–89	90–113	114–128	129–151	152–166
Hu M-CSF	1–14	15–38	39–45	46–61	62–72	73–93	94–109	110–130	131–522
Mu M-CSF	1–14	15–38	39–45	46–61	62–72	73–93	94–109	110–130	131–520

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